STUDIES ON THIENO[3,4-*d*]PYRIDAZINE AND ELECTRON ACCEPTOR COMPOUNDS

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Abstract : Ethyl 5-anuno-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate **1a,b** gave N,N^1-di(ethyl-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate)hydrazine and N,N^1-di(ethyl-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate)aminocyanomethaneimine as well as di(ethyl-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate)amine when reacted with tetracyanoethylene (TCNE), 2-(dicyanomethyleneindane-1,3-dione) (CNIND) and 1,4-benzo- as well as 1,4-naphthoquinone.

Introduction

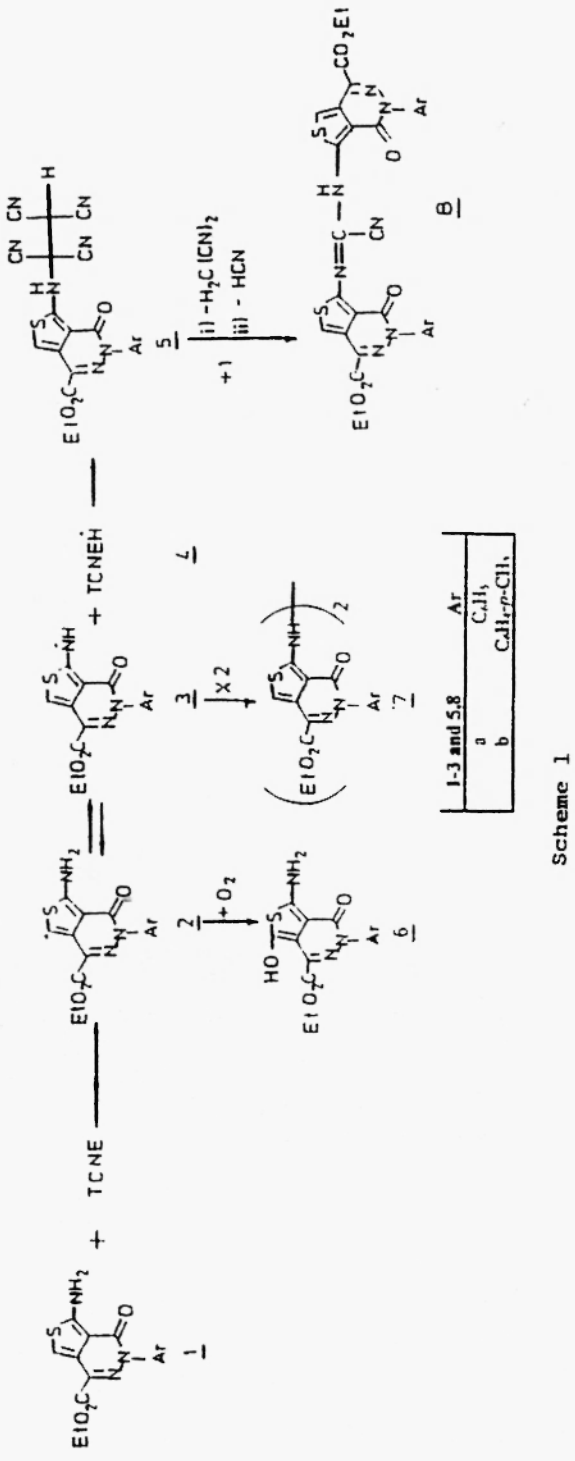
It is well documented that, thiophene and its derivatives are reluctant partners in [4+2] cycloadditions with dienophiles containing a double bond (1-4). Döpp and co-workers reported that, 3-amino-4-imino-4H-thieno[3,4-c][1]benzopyran added dimethyl maleate and dimethyl acetylenedicarboxylate in a [4+2] mode across the thiophene ring to form benzo[3,4-*c*][1]benzopyran-2,3-dicarboxylate as well as thiepin derivatives (5). Moreover, thieno[3,4-d]pyridazines **1** were found highly reactive towards activated double bond systems. Thus, phthalazine carboxylates and phthalazine dicarboxylates as well as phthalazine anhydrides were obtained on treating **1** with acrylonitrile, ethyl acrylate and maleic anhydride respectively (6-8).

Our interest on the chemistry of organosulfur with π-deficient substances (9-13), as well as benzothiophene with captodative alkenes (14) prompted us to investigate the behaviour of ethyl 5-amino-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-d]pvridazine-1-carboxylate **1a,b** (6) towardes some π-acceptors.

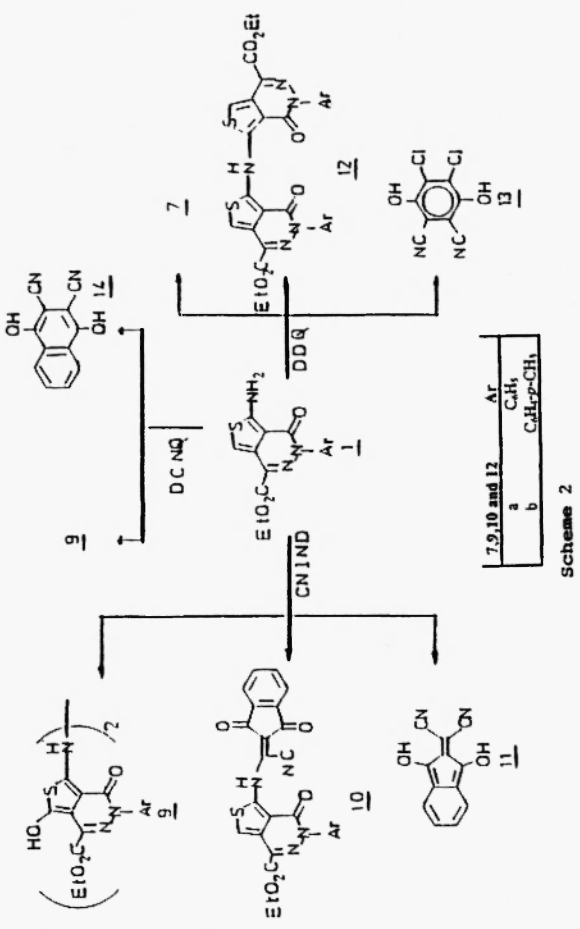
Results and Discussion

When ester **1** was allowed to react with tetracyanoethylene (TCNE) in ethyl acetate, a mixture of several products was obtained in a combined yield 68-70 % (Scheme 1), following chromatographic separation, the method used allowed the formation of three products namely ethyl 5-amino-7-hydroxy-3-4-dihydro-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate **6** (11-13%), N,N^1-di(ethyl-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-d]pyridazine-1-carboxylate)hydrazine **7** (38-40%) and N,N^1-di(ethyl-3,4-dihydro-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate)aminocyanomethaneimine **8** (18-19%). Assignment of the structure of compounds **6-8** was based on their spectral data and the combustion analysis. The elemental analysis of **8a**, as example, showed the gross formula $C_{32}H_{23}N_7O_6S_2$ was deduced from results. This was confirmed by the mass spectrum which exihibted a molecular ion at m/z 665 (18%). The IR spectrum showed absorption bands at 3367, 2218 and 1718 characteristic for NH, CN, and CO respectivily. The ^{1}H-NMR spectrum exihibted broad singlet at δ= 7.85 ppm due to NH besides signals due to thiophene- CH, ethoxy group and aryl protons.

The rationalization of the reaction products based on initial formation of unstable CT-complexes between **1** and TCNE followed by formation of the radicals **2-4** and the adduct **5**, the latter adduct reacted with another molecule of **1** to form **8**, via elimination a molecule of malononitrile and another of HCN (10,15) (detected by Ferrithiocyanate test) (16).



Scheme 1



Scheme 2

Attack of aerial oxygen on radical **2**· proceeds to **6**, in presence of hydrogen atom sources such as **1**. Whereas the formation of dimer **7** require the intermediate formation of thienopyridazine radicale **3**·. The formation of compounds **6** and **7** supported the existance of the two isomeric radical **2**· and **3**· . The participation of moist air in formation of compound **6** as illustrated in the proposed mechanism in Scheme 1 was confirmed by adding the ester **1** to TCNE under nitrogen and dry conditions, only CT- complex was formed which dissociate into its components after time and do not follow the given reaction sequence. In order to provide further support for the validity of the reaction pathway and any further reactions between compounds **6,7** and TCNE, upon adding doubled molar amounts of TCNE to one mole of solution **1** followed by sublimation the unreacted TCNE and chromatographic separation the reaction mixture gave the products which isolated when equimolar amount of **1** and TCNE were interacted.

On the other hand, mixing compound **1** with 2-(dicyanomethyleneindan-1,3-dione) (CNIND) or 2,3-dicyano-1,4-naphthoquinone (DCNQ) in ethyl acetate and chromatographic isolation of the mixtures after 4 days, yielded both reactants only . On mixing CNIND or DCNQ and **1** in DMF (which is presumable tend to increase the interactions between the components) an initial CT- complexes was formed and subsequent chemical reaction took place within 72 h. at room temperature in presence of air. CNIND interacted with **1a,b** in DMF afford the highly predominant products di(ethyl-3,4-dihydro-7-hydroxy-4-oxo-3-aryl-thieno[3,4-*d*]pyridazine-1-carboxylate)hydrazine **9** and thieno[3,4-*d*]pyridazine(1,3-dioxo-2-indanylidene)acetonitrile derivatives **10** (Scheme 2), in addition to 1,3-dihydroxy-2H-(inden-2-ylidene) malonitrile **11** (17) , as a minor product. From ^{1}H-NMR spectra of compound **10**, the integration of aromatic protons confirm the presence of thiophene-CH proton and the absence of any broad band at δ= 7.0 ppm due to NH_2 group attatched to thiophene ring (6). On the other hand, the absence of thiophene-CH in **9** and the presence of OH group, gave the assignment of structure **9**.

Although, the electron affinity of TCNE or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is higher than that of CNIND or DCNQ(18) , the interaction between TCNE or DDQ with **1** results in formation of dehydrodimer **7**, whereas with CNIND or DCNQ further oxidation and hydroxylated compound **9** was formed . This behaviour confirm the participation of DMF as the solvent in the reaction, which increase the interactions between components.

Conclusion

From the above findings, it may be concluded that , although the amino function in **1** renders the thiophene ring sufficiently electron rich to act as a diene in a [4+2] cycloadditions and TCNE (which is not only a patent dienophile in Diels-Alder reactions but is also amenable to both [4+2] and [2+2]cycloadditions) (19,20) the results obtained in the present investigation clearly shows that TCNE, CNIND and benzo-, as well as naphthoquinones interacted as a hydrogen abstractor to form aforementioned compounds.

Experimental

All melting points were measured on an electrically heated Griffin Capillary Melting Piont Apparatus and are uncorrected. The IR spectra were recorded using Shimadzo 470 spectrophotometer. ^{1}H-NMR spectra were obtained with a Bruker WM300 (300 MHz), with TMS as an internal standard. Mass spectra: AMD 604. Microanalysis were carried out by Microanalysis centre at Cairo University. Preparative layer chromatography (PLC) has been carried out on 48 cm wide and 20 cm high glass plates and air dried silica gel Merck Pf_{254}.

Materials.- Ethyl 5-amino- 3,4-dihydro-4-oxo-3-aryl-thieno[3,4-d]pyridazine-1-carboxylate was prepared according to the literature (6) . TCNE, DDQ, CNIND and DCNQ were prepared and purified as reported before (10).

Reaction of TCNE with 1a,b .- To a solution of TCNE (128 mg, 0.001 mol) in 10 ml dry ethyl acetate , a solution of 0.001 mol of **1a,b** in 15 ml of dry ethyl acetate was added with stirring at room temperature. The stirring was continued for 5h., and then allowed to stand for 72h.(the reaction products were followed by TLC), during which , brown crystals were separated. The resulting solid product was filtered, washed with ethanol, dried and recrystallized from DMF/ethanol to give **7a,b**. The filtrate was evaporated

and the residue was chromatographed on PLC using cyclohexane/ ethyl acetate (4:1) as eluent to give two zones. the fastest migrating one contained compound **6** and the second zone which characteristic with deep blue colour contained **8** . The products **6** and **8** were extracted with acetone and recrystallized from the appropriate solvent (Table II).

Reaction of CNIND with ***1a,b*** - To a solution of 416 mg (0.002 mol) of CNIND in 10 ml of DMF, **1a,b** (0.001 mol) in 10 ml of DMF were added at room temperature and the stirring was continued for another 72h., during which, the orange crystals of **10** was separated. Concentration of the filtrate and chromatographic purification of the residue using toluene / ethyl acetate (5:1) as eluent afforded two zones, the fastest migrating one contained 1,3-dihydroxy-2H-(inden-2-ylidene)malonodinitrile **11**(11%) (15). The second zone contained compound **9** . The zones were extracted with acetone and recrystallized from appropriate solvent (Table II).

Reaction of DDQ with ***1a,b*** .- To asolution of 227 mg (0.001 mol) DDQ in 10 ml of dry ethyl acetate, thienopyridazine **1a,b** (0.001 mol) in 15 ml dry ethyl acetate was added dropwise with stirring at room temperature. The reaction mixture was stirred for another 48h., and then filtered off. The precipitate was washed with ethanol and recrystallized from a suitable solvent to give compound **12**. The filtrate was concentrated and the residue was then chromatographed on PLC using toluene/ethyl acetate (5:1) as eluent to give two zones. The fastest migrating one contained compound 7 (28-30%), the second zone contained the dihydroquinone **13** (40 mg, 17%). The zones were extracted with acetone and recrystallized from appropriate solvent (Table II).

Reaction of DCNQ with ***1a,b*** - To a solution of 416 mg (0.002 mol) DCNQ in 15 ml DMF, a solution of (0.001 mol) **1a,b** in 10 ml DMF was added at room temperature. Then the reaction mixture,was stirred for 72h., evaporated and the residue was chromatographed on PLC using toluene/ ethyl acetate (5:1) as eluent to give two zones . The fastest migrating one contained compound 9 (36-39%), the second zone contained the dihydroquinone **14** (66 mg, 31%). The zones were extracted and recrystallized from the suitable solvent.

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Table I: The ^{1}H-NMR, IR and MS spectral data of compounds **6-10 and 12**.

Compound	^{1}H-NMR (δ, TMS)*	IR (KBr, ν)**	MS m/z (rel.intensity %)
6a	1.33(t,3H, Ar-H), 4.21(q, 2H, CH_2), 7.05(br, 2H, NH_2, D_2O exchangeable 7.30-7.60(m, 4H, Ar-H), 7.62-7.66(m, 1H, Ar-H), 11.22(br, 1H, OH).	3488(s, OH), 3415, 3325(w, NH_2), 1735(s, CO).	331(M^+, 44), 314(7), 286(14), 137(7), 93(100).
6b	1.30(t, 3H, CH_3), 2.17(s, 3H, CH_3), 4.18(q, 2H, CH_2), 7.00(br, 2H, NH_2), 7.24-7.33(d, 2H, Ar-H), 7.40-7.51 (m, 1H, Ar-H), 7.53-7.60(m, 1H, Ar-H), 11.17(br, 1H, OH).	3485(s, OH), 3400, 3315(w, NH_2), 1730(s, CO).	345(M^+, 53), 328(3), 299(5), 256(6), 121(100), 107(10), 93(11)..
7a	1.31(t, 6H, 2 CH_3), 4.20(q, 4H, 2 CH_2), 7.22-7.55(m, 8H, Ar-H), 7.57-7.63(m, 4H, Ar-H and thiophene-CH), 7.84(br, 2H, 2 NH).	3412-3302 (NH), 2987 (Ali-CH), 1714 (CO).	628(M^+, 100), 600(5), 510(4), 483(11), 315(13), 259(4), 242(4), 93(23), 77(39).
7b	1.28(t, 6H, 2 CH_3), 2.20(s, 6H, 2 CH_3), 4.16(q, 4H, 2 CH_2), 7.20-7.34(d, 4H, Ar-H), 7.42-7.50(m, 2H, Ar-H), 7.53-7.60(m, 4H, Ar-H and thiophene-CH), 7.79(br, 2H, 2 NH)..	3395-3339(NH), 1715(CO).	656 (M^+, 14), 628 (7), 572 (3), 542 (3), 396 (5), 332 (36), 108 (70), 44 (100).
8a	1.30(t, 6H, 2 CH_3), 4.20(q, 4H, 2 CH_2), 7.36-7.58(m, 8H, Ar-H), 7.61-7.70(m, 4H, Ar-H and thiophene-CH), 7.85(br, 1H, NH, D_2O exchangeable).	3367-3263(NH), 2218(CN), 1718(CO).	665(M^+, 18), 664(19), 648(15), 631(6), 594(5), 592(9), 578 (7), 566 (8), 552 (8), 537 (8), 416 (50), 342 (38), 149 (60), 44 (100).
8b	1.27(t, 6H, 2 CH_3), 2.18(s, 6H, 2 CH_3), 4.18(q, 4H, 2 CH_2), 7.32-7.40(d, 4H, Ar-H), 7.49-7.54(m, 2H, Ar-H), 7.58-7.66(m, 4H, Ar-H and thiophene-CH), 7.80(br, 1H, NH).	3376-3246(NH), 2228(CN), 1722(CO).	693(M^+, 14), 663(27), 607(11), 461(32), 405(21), 91(63), 44(100).
9a	1.25(t, 6H, 2 CH_3), 4.15(q, 4H, 2 CH_2), 7.35-7.52(m, 8H, Ar-H), 7.53-7.60(m, 2H, Ar-H), 7.70(br, 2H, 2 NH), 11.28(br, 2H, 2 OH).	3472-3318(OH, NH), 2978, 2929(Ali-CH), 1730(CO).	660(M^+, 10), 628(18), 626(12), 330(23), 93(88), 44(100).
10a	1.32(t, 3H, CH_3), 4.21(q, 2H, CH_2), 7.22-7.58(m, 8H, Ar-H), 7.60- 7.66(m, 2H, Ar-H and thiophene-CH), 8.18(br, 1H, NH)..	3238(NH), 2236(CN), 1708, 1662(CO)..	496(M^+, 84), 469(7), 468(9), 440(5), 397(20), 396(19), 368(14), 352(19), 315(27), 221(12),137(21), 126(16), 104(42), 77(100), 44(97).
12a	1.26(t, 6H, 2 CH_3), 4.18(q, 4H, 2 CH_2), 7.24-7.54(m, 8H, Ar-H), 7.56-7.60(m, 4H, Ar-H,and thiophene-CH), 7.81(br, 1H, NH).	3366(NH), 1726(CO).	613(M^+, 4), 611(6), 537(4), 509(11), 481(8), 453(9), 437(10), 410(3), 315(20), 287(4), 119(94), 93(89), 44(100).
12b	1.22(t, 6H, 2 CH_3), 2.22(s, 6H, 2 CH_3), 4.16(q, 4H, 2 CH_2), 7.20-7.30(d, 4H, Ar-H), 7.38-7.49(m, 2H, Ar-H), 7.51-7.60 (m, 4H, Ar-H and thiophene-CH), 7.77(br, 1H, NH).	3387(NH), 1720(CO).	641(M^+, 7), 570(14), 497(16), 329(33), 133(66), 93(77), 44(100).

* All compounds were measured in DMSO-d_6 except compounds 8a,b and 9a,b in $CDCl_3$.

** IR spectra were recorded using potassium bromide pellets except compounds 6a and 6b in CCl_4.

Table II: Physical and analytical data of compounds **6-10** and **12**

Compound	m.p. °C	Yield %	Colour	Solvent of recrystallization	Mol. Formula (M. Wt.)	Analysis % Found (Calcd) C	H	N	S
6a	296-298	11	Pale yellow	Ethanol	$C_{15}H_{13}N_3O_4S$ (331.345)	54.19 (54.37	4.12 3.95	12.54 12.68	9.81 9.68)
6b	318-320	13	Pale yellow	Ethanol	$C_{16}H_{15}N_3O_4S$ (345.372)	55.76 (55.64	4.21 4.38	12.33 12.17	9.12 9.28)
7a	250-252	38	Brown	DMF/Ethanol	$C_{30}H_{24}N_6O_6S_2$ (628.536)	57.14 (57.32	3.71 3.85	13.52 13.37	10.33 10.20)
7b	236-238	39	Brown	DMF/Ethanol	$C_{32}H_{28}N_6O_6S_2$ (656.730)	58.68 (58.53	4.18 4.30	12.66 12.80	9.83 9.76)
8a	179-181	19	Blue	Ethanol	$C_{32}H_{23}N_7O_6S_2$ (665.697)	57.59 (57.74	3.69 3.48	14.61 14.73	9.78 9.63)
8b	205-207	18	Blue	Ethanol	$C_{34}H_{27}N_7O_6S_2$ (693.751)	58.69 (58.86	4.12 3.92	13.94 14.13	9.37 9.24)
9a	170-172	16	Yellow	Ethanol	$C_{30}H_{24}N_6O_8S_2$ (660.675)	54.63 (54.54	3.48 3.66	12.55 12.72	9.88 9.71)
9b	236-238	14	Yellow	Ethanol	$C_{32}H_{28}N_6O_8S_2$ (688.729)	55.63 (55.81	4.26 4.10	12.37 12.20	9.23 9.31)
10a	348-350	41	Orange	DMF/Ethanol	$C_{26}H_{16}N_4O_5S$ (496.496)	63.07 (62.90	3.33 3.25	11.11 11.28	6.61 6.46)
10b	325-327	43	Orange	DMF/Ethanol	$C_{27}H_{18}N_4O_5S$ (510.523)	63.36 (63.52	3.41 3.55	11.16 10.97	6.44 6.28)
12a	342-344	21	Brown	DMF/Ethanol	$C_{30}H_{23}N_5O_6S_2$ (613.662)	58.56 (58.72	3.98 3.78	11.24 11.41	10.63 10.45)
12b	319-321	24	Brown	DMF/Ethanol	$C_{32}H_{27}N_5O_6S_2$ (641.715)	60.14 (59.89	4.31 4.24	10.77 10.91	10.16 9.99)